REMARKS

Claims 1-25 were pending in this application. Claims 1-6 and 14-25 have been withdrawn from consideration as being drawn to a non-elected invention. Claims 7-13 were under examination. Claims 26-31 have been added to more clearly describe the claimed invention. Support for these amendments and the new claims can be found throughout the specification as filed, including: on page 2, lines 22-29 and page 26, lines 21-31 (claim 26); one page 2, lines 30-32 (claim 27); on page 2, lines 32-33 (claim 28); on page 2, lines 34-35 (claim 29); on page 3, lines 1-2 (claim 30); on page 3, lines 3-5 (claim 31) and elsewhere throughout the specification. Attached hereto is "Version with markings to show changes made" which shows the changes made to the claims by the current amendment. No new matter is believed added.

In light of the following remarks, Applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Objections to Claims

Claim 13 is objected to because of the use of the phrase "comprise amino acid residues 1471-1573 of the HCV polypeptides." This is characterized as a typographical error because it is not associated with any claimed language.

Applicants submit that claim 13, as amended deletes the phrase over which the claim was objected to. In particular, the mistake of a typographical nature has been corrected by the amendment. Applicants request removal of this basis of objection.

II. Rejections under 35 U.S.C.§ 112, second paragraph

Claims 7-13 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

A. Specifically, claim 7 is allegedly unclear "for recitation of HCV and NS."

Applicants submit that claim 7, as amended to spell-out the full names of the hepatitis C virus and the nonstructural proteins, is not indefinite. Applicants request removal of this ground of rejection.

B. Specifically, claim 7 is allegedly vague and indefinite in that the metes and bounds of "one or more antigen epitopes" are not defined. The Examiner, citing *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993), indicates that although the claims are interpreted in the light of the specification, limitations from the specification are not read into the claims. Further, the Examiner states that "because there are many antigen epitopes in the regions of the HCV core, NS3 and NS4 proteins, the claims should point out which epitope is intended in the said claim."

Applicants agree with the Examiner that, as held in *In re Van Geuns*, limitations from the specification are not to be read into the claims, but that claims are to be given their broadest meaning. Accordingly, Applicants request that the claims be given their broadest meaning and then be examined on that basis. In particular, Applicants request that claims reciting "one or more antigenic epitopes of each of the...," should in strict accordance with *In re Van Geuns* be given their broadest possible meaning, namely, that the polypeptide of the invention includes at least one antigenic epitope from each of the proteins listed. This, while inclusive of many different embodiments of the invention, is not vague. Nor is it indefinite, as the metes and

bounds of the invention are clear, precise and defined, particularly in light of the content of the application, the teachings of the prior art, and the claim interpretation that would be given by one of the ordinary level of skill in the art. Any further explanation or limitation, such as that suggested by the Examiner "to point out which epitope is intended in the said claim" is neither necessary for one of ordinary skill in the art to determine the claimed invention with clarity and precision, nor required under the law to fulfill the requirement that the claims be definite. Applicants, therefore, request removal of this basis of rejection.

C. Specifically, claims 7-13 are allegedly rendered indefinite for reciting "comprising" to define the mosaic peptide structure and antigen epitope structure. This is because the word "comprising" is open language which "fails to define any precise amino acid sequence structure." The Examiner indicates that the claims should use more defined language to describe the novelty of the intended amino acid sequence of the peptide or epitope in the said claims.

Applicants submit that use of "open-ended" language such as comprising does not render the claims indefinite. It appears to the Applicant that the Examiner is seeking to require that all structure of any composition of the invention be precisely, and explicitly, defined in each claim. Further, in seemingly requiring that the Applicants use "more defined" language, the Examiner appears to infer that the Applicants should narrow the scope of the claims to cover, not a "polypeptide comprising one or more antigenic epitopes...," but rather a polypeptide of, or containing, a particular amino acid sequence. If this is the intent of the Examiner's position, Applicants submit that the Examiner is not properly requiring definiteness, but rather the Examiner is improperly seeking to limit the breadth of the claims. While the present claims are of significant breadth, they are not indefinite. Breadth of a claim is not to be equated with indefiniteness. *In re Miller*, 441 F.2d 689, 169 USPQ 597 (CCPA 1971). Applicants request removal of this basis of rejection.

III. Rejections under 35 U.S.C.§ 102

A. Claim 7 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chien et al. (a) (PNAS USA (1992)). Specifically, Chien et al. teaches a fusion protein comprising a sequence that includes sequence from the nucleocapsid protein C, NS3 protein, and NS4 protein.

Applicants submit that Chien et al. (a) does not anticipate the present invention, particularly as recited in amended claim 7. Specifically, Chien et al. discloses a fusion protein (C25 chimeric polypeptide) that includes sequence from the C33C, C100-3 and C22 recombinant polypeptides. Claim 7 has been amended to recite, in pertinent part, "...wherein at least two antigenic epitopes are from the same region of variants of the same protein." Support for the amendment of claim 7 can be found, *inter alia*, on page 2, lines 23-29, wherein the preferred mosaic polypeptides are described as containing antigenic epitopes from the core protein, NS3 protein and NS4 protein." As the present application specifically defines the terms "a," "an," and "the" to mean one or more and to include the plural unless the context is inappropriate (page 7, lines 26-28), the description from page 2, lines 23-29, must necessarily be interpreted by one of ordinary skill in the art to also include those mosaic polypeptides containing more than one antigenic epitope from the same region of the core protein, NS3 protein or NS4 protein. Furthermore, the recitation of the different types of relationships between different antigenic epitopes that can be included in the antigenic epitopes and mosaic polypeptides make it clear to one of skill in the art that the different antigenic epitopes contemplated include those wherein the epitopes are derived from the same region of the same protein from different species, as "...allelic, strain, or species variants..." necessarily indicates inclusion of multiple sequences from non-identical variants (see page 26, lines 21-31). Unlike claim 7 as amended, the C25 chimeric polypeptide does not include a second antigenic epitope from corresponding regions of any of the three proteins recited (i.e., the core, NS3 and NS4 proteins).

As claim 7, as amended, is not anticipated by Chien et al.(a), Applicants request removal of this basis of rejection.

B. Claims 7 and 8 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chien et al.(b) (J. Gastro. Hepato. 1993, Vol. 8, pp. S33-39). Specifically, it is alleged that Chien et al. teach a general method for using recombinant antigen polypeptide antigen (C25) comprising six proteins representing the structural regions of core, the envelope and non-structural regions (C33C) and NS3-NS4 (C11-3) and NS5 to detect the anti-HCV antibody. The general method, using the combined antigens was deemed superior to using the single peptide assay.

Applicants submit that Chien et al. (b) does not anticipate the present invention, either as is now recited in amended claim 7, or as is now or was previously recited in claim 8. As the C25 antigen disclosed in Chien et al (b) appears indistinguishable from the C25 antigen disclosed in Chien et al. (a) (both are C33C-C100-C22 of 858 amino acids), Applicants submit that the same arguments and bases for establishing the novelty of claim 7 over Chien et al. (a) are also applicable for, and sufficient in, establishing the patentability of claim 7 over Chien et al. (b). Accordingly, Applicants reiterate the above response to the rejection of claim 7 over Chien et al. (a) above and request removal of this basis of rejection for amended claim 7.

Further, Applicants submit that the facts in Chien et al. (b) have been mischaracterized. While it is alleged in the Office Action that Chien et al. (b) teaches that the C25 antigen comprises six proteins, including the NS5 protein, it does not. As stated in the middle of the first paragraph on page S34:

> "Seven discrete protein coding regions were expressed... six were encoded from the core (C22-3), the envelope (E1 and E2), and non-structural NS3 (C33c), NS3-

NS4 (C100-3) and NS5 regions. The seventh was a chimeric protein, C25, encoding an SOD/C33C-C11-C22 fusion."

Thus, as stated in Chien et al. (b), the seven protein coding regions are: (1) C22-3 from the core; (2) E1 from the envelope; (3) E2 from the envelope; (4) C33C from NS3; (5) C100-3 from NS3-NS4; (6) NS5; and (7) C25 from the fusion of C33 from NS3, C100 from NS3-NS4, and C22 from the core. In this context, it is clear that Chien et al. (b) refers to the first six protein coding regions as separate protein coding regions, not as any chimera comprising two or more of these coding regions. Furthermore, it is clear that the C25 fusion, the seventh protein coding region, includes only sequence from NS3, NS4 and the core proteins. The C25 fusion includes no NS5 sequence. Because no protein comprising NS3, NS4, NS5 and core antigen is disclosed in Chien et al., it cannot anticipate claim 8 as that claim requires "one or more antigenic epitopes from NS5a." Applicants request removal of this basis of rejection and request that this basis of rejection not be applied to new claims 26-31, which all include an NS5a epitope.

Specifically, as new claims 26-31 require "...one or more antigenic epitopes of each of the HCV core protein, NS3 protein, NS4 protein and NS5a protein," they cannot be anticipated by Chien et al. as Chien et al. does not disclose any mosaic polypeptide having NS5a protein.

C. Claims 7 and 8 are rejected 35 U.S.C. § 102(b) as allegedly anticipated by Valenzuela et al. (WO 97/44469 A2). Specifically, Valenzuela et al. teach a multiple copy epitope sequence that can include regions selected from the group consisting of, among others, core, NS3, NS4, and NS5 proteins.

Applicants submit that Valenzuela et al., published on November 27, 1997, does not properly constitute a basis for anticipation of the present application under 35 U.S.C. § 102(b) as

the publication of Valenzuela et al. does not predate by more than one year the date of the application for patent in the United States. Specifically, the present application claims priority to PCT/US99/15578 filed July 9, 1999, which claims priority to Provisional Application Serial Number 60/092,339 filed July 10, 1998, less than one year after the publication of Valenzuela et al. Further, as evidenced by the attached declaration, the invention of the presently claimed invention predates the date that Valenzuela et al. published, namely, November 27, 1997. Correspondingly, claims 7 and 8 are not anticipated by Valenzuela et al. Applicants request removal of this basis of rejection.

IV. Rejection under 35 U.S.C. § 103

A. Claims 7, and 9-12 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Chien et al. (a) and Kato et al. Specifically, it is alleged that Chien et al., which teach a fusion protein comprising the sequence structures of certain NS3 fragments, NS4 fragments and nucleocapsid protein C (core) fragments, render the present invention obvious. The present invention, as described incorrectly in the Office Action, is purported to be a mosaic polypeptide comprising one or more epitopes from each of the HCV core, NS3 and NS4 proteins, wherein the core is amino acids sequence 1-91, NS3 are 1471-1573 and 1789-1867, NS4 are 1789-1867 and 1916-1948. These sequences are acknowledged to differ from those used by Chien et al. However, the Examiner asserts that the claimed structures of the HCV are known in the art as evidenced by Kato et al. who disclose all the claimed sequences from claims 7 and 9-12 with 100% homology.

Further, it is alleged that it would have been obvious to one of ordinary skill in the art at the time the invention was filed to be motivated by the reference of Chien et al. (a) and further in view of the sequences disclosed by Kato et al. to make a mosaic polypeptide comprising HCV core, NS3 and NS4 for detecting anti-HCV antibodies with improved sensitivity. Hence, it is

concluded by the Examiner that the claimed invention as a whole is prima facie obvious absent unexpected results.

In response, Applicants submit that the characterization of the present invention as being "a mosaic polypeptide .... wherein the core is amino acids sequence 1-91, NS3 are 1471-1573 and 1789-1867, NS4 are 1789-1867 and 1916-1948" is incorrect. In particular, the characterization of the present invention in the Office Action is too narrow. The present invention, particularly as recited in amended claim 7, is not limited to any specific subset of: the core, such as amino acid residues 1-91; the NS3 protein, such as amino acid residues 1471-1573; or the NS4 protein, such as 1789-1867 and 1916-1948. The present invention as recited in amended claim 7 can include any antigenic epitope from the HCV core protein, NS3 protein or NS4 protein so long as at least one antigenic epitope is included from each and wherein at least two antigenic epitopes are from corresponding regions of variants of the core protein, NS3 protein or NS4 protein. Correspondingly, that the particular sequences in Chien et al. may not match particular examples disclosed in the present application, or that there is some putative correspondence between the sequence of Kato et al. and sequences used in particular examples disclosed in the present application, is of no relevance. Claim 7 as amended, and claims 9-12 dependent therefrom, are directed to a mosaic polypeptide that includes "at least two antigenic epitopes... from the same region of variants of the same protein." This limitation, or its desirability, is neither taught nor suggested by the cited references. Correspondingly, Chien et al. (a) and Kato et al. can not properly establish a *prima facie* case of obviousness for this invention. Specifically, they do not fulfill the three criteria that must be met for a *prima facie* case of obviousness to be established, namely, (1) some suggestion or motivation to combine reference teachings; (2) a reasonable expectation of success; and (3) the combination of references must teach or suggest all claim limitations.

As it relates to the first criterion, there is no teaching in either Chien et al. (a) or in Kato et al. that the assay of Chien et al. is deficient or requires further sequence. Correspondingly, there can be no motivation to combine Kato et al. with Chien et al. Since NS5 was known to Chien et al. (a), Kato provides no motivation to add it to the C25 protein of Chien et al. Furthermore, even if there was a teaching that Chien et al. was deficient, without further teaching or guidance as to making the combination with Kato et al., a rejection based upon a finding of *prima facie* obviousness is improper. The PTO can satisfy its burden of establishing a prima facie case of obviousness "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, U.S.P.Q.2d 1596 (Fed. Cir. 1988). Thus, the first required criterion is not met.

Rather, there is only an unsupported conclusion *on the part of the Examiner* that making a "mosaic polypeptide comprising HCV core, NS3, NS4 and NS5" polypeptide would result in improvements in the art. As such, this statement is clearly not a recitation of any motivation or suggestion *within the teachings of the art* to combine the cited references. The cited publications do not reach this conclusion nor suggest it. The Examiner's conclusion, in fact, is only a cautionary example of the hindsight-based obviousness analysis against which the proper standards of determining obviousness have been developed to guard against and against which the courts warn. "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998).

As it relates to the second criterion, Applicants submit that in order for there to be a reasonable expectation of success, there must at least be a suggestion or motivation to provide a combination of elements that provides the present invention. Indeed, without any such

motivation or suggestion, there can be not only no reasonable expectation of success, there can be no expectation of success. Thus, the second required criterion is not met.

As it relates to the third criterion, there is no example of a chimeric protein in either cited reference having antigenic epitopes from the same region of variants of the same protein, nor is there any suggestion of including antigenic epitopes from the same region of variants of the same protein. Correspondingly, provision of any number of examples having only one antigenic epitope from any given region of any given protein can not render the present invention *prima facie* obvious no matter how many different sequences are provided. Applicants therefore request removal of this basis of rejection.

B. Similarly, Claims 7-13 are rejected under 35 U.S.C. § 103(a) over Chien et al. (b) and Kato et al. It is alleged that Chien et al. teaches a general method for using the C25 recombinant polypeptide antigen, that the C25 antigen comprises "six proteins representing the structural regions of core, the envelope and non-structural regions (C33C) and NS3-NS4 (C11-3) and NS5" and that the C25 assay was considered superior to the single peptide assay. It is acknowledged that Chien et al. does not disclose precise amino acid sequences, however it is alleged that these sequences are known in the art, specifically as evidenced by Kato et al.

Further, it is stated in the Office Action that it:

> "to get better sensitivity for detecting the HCV infection or to get better immunogenicity for inducing an immune response, it would have been obvious to one of ordinary skill in the art at the time of the invention was filled to be motivated by the recited reference of Chien et al (b) and in further view of sequence the disclosed by Kato et al to make a mosaic polypeptide comprising HCV core, NS3, NS4 and NS5 for detecting the anti-HCV antibodies with an

improved higher sensitivity without unexpected results. Hence, the claimed invention as a whole is prima facie obvious absence unexpected results."

In response, Applicants again submit that the characterization of Chien et al. (b) is incorrect. As outlined above in section II.B., the C25 fusion includes only sequence from NS3, NS4 and the core proteins. The C25 fusion includes no NS5 sequence.

Claim 7 as amended, and claims 9-12 dependent therefrom, are directed to a mosaic polypeptide that includes "at least two antigenic epitopes... from the same region of variants of the same protein." This limitation, or its desirability, is neither taught nor suggested by the cited references.

Claim 8, claim 13 dependent therefrom, new claim 26, and new claims 27-31 dependent therefrom, are directed to a mosaic polypeptide that includes "one or more antigenic epitopes of the HCV NS5a protein." This limitation, or its desirability, is neither taught nor suggested by the cited references.

Correspondingly, Chien et al. (b) and Kato et al. can not properly establish a prima facie case of obviousness for this invention. Specifically, they do not fulfill the three criteria that must be met for a *prima facie* case of obviousness to be established, namely, (1) some suggestion or motivation to combine reference teachings; (2) a reasonable expectation of success; and (3) the combination of references must teach or suggest all claim limitations.

As it relates to the first criterion, namely, that there be some suggestion or motivation to combine reference teachings; there is no teaching in either Chien et al. (b) or in Kato et al. that the assay of Chien et al. is deficient or requires further sequence. Correspondingly, there can be no motivation to combine Kato et al. with Chien et al. Since NS5 was known to Chien et al. (b),

Kato provides no motivation to add it to the C25 protein of Chien et al. Furthermore, even if there was a teaching that Chien et al. was deficient, without further teaching or guidance as to making the combination with Kato et al., a rejection based upon a finding of prima facie obviousness is improper. The PTO can satisfy its burden of establishing a prima facie case of obviousness "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." *In re Fine*, 837 F.2d 1071, U.S.P.Q.2d 1596 (Fed. Cir. 1988).

This requirement for objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art is not fulfilled by the present combination of references, notwithstanding the Examiner's conclusion that "it would have been obvious to one of ordinary skill in the art at the time the invention was filed (sic) to be motivated by the recited reference of Chien et al. (b) ...to make a mosaic polypeptide comprising HCV core, NS3, NS4 and NS5" in order "to get better sensitivity for detecting the HCV infection or to get better immunogenicity." Indeed, there is no basis or support here for a finding of obviousness. There is only an unsupported conclusion *on the part of the Examiner* that making a "mosaic polypeptide comprising HCV core, NS3, NS4 and NS5" polypeptide would result in improvements in the art. As such, this statement is clearly not a recitation of any motivation or suggestion *within the teachings of the art* to combine the cited references. The cited publications do not reach this conclusion nor suggest it. The Examiner's conclusion, in fact, is only a cautionary example of the hindsight-based obviousness analysis against which the proper standards of determining obviousness have been developed to guard against and against which the courts warn. "Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." *In re Dance*, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998).

As it relates to the second criterion, Applicants submit that in order for there to be a reasonable expectation of success, there must at least be a suggestion or motivation to provide a combination of elements that provides the present invention. Indeed, without any such motivation or suggestion, there can be not only no reasonable expectation of success, there can be no expectation of success. Thus, the second required criterion is not met.

As it relates to the third criterion, namely, that the combination of references must teach or suggest all claim limitations; there is no teaching or suggestion for any mosaic polypeptide that includes "at least two antigenic epitopes... from the same region of the same protein" or for any that includes "one or more antigenic epitopes of the HCV NS5a protein." Consequently, claim 7 as amended, and claims 8-13 dependent therefrom, and new claim 26, and new claims 27-31 dependent therefrom, are not *prima facie* obvious. Applicants therefore request removal of this basis of rejection for all pending claims.

C. Claims 7-13 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Valenzuela et al. and in further view of Chien et al.(b) and Kato et al. Specifically, Valenzuela et al. teach a multiple epitope sequence having the general structural formula (I): (A)x-(B)y-(C)z, wherein the (I) is a linear amino acid sequence and the A. B. and C, are epitopes from regions of the HCV polyprotein (e.g., NS3, NS4, and NS5).

Applicants submit that Valenzuela et al., published on November 27, 1997, does not properly constitute a basis for a finding of obviousness of claims 7-13 of the present application under 35 U.S.C. § 103 as the presently claimed invention was conceived prior to the publication of Valenzuela et al. as evidenced by the attached declaration of the Applicants. Applicants therefore request removal of this basis of rejection.

In summary, the cited references, Chien et al. (a), Chien et al. (b), Kato et al., and Valenzuela et al. do not fulfill even one of the three criteria which must be met in order to properly establish a *prima facie* case of obviousness. Specifically, Valenzuela et al. cannot properly be used as a basis for obviousness as the invention claimed was conceived prior to its publication. Specifically, Chien et al. (a), Chien et al. (b) and Kato et al., do not fulfill any criteria for a proper basis of obviousness. Correspondingly, Applicants respectfully request removal of the bases of rejection that rely on obviousness.

In regard to claims 8-13 and 27-31, all dependent from independent claims to which each of the above remarks apply, the Applicants refer the Examiner to the MPEP § 2143.03, 1st paragraph, wherein it states, "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)." Accordingly, so as to not unduly burden the Examiner, the Applicants will refrain from presenting additional arguments and support for the nonobviousness of the various dependent claims at the present time. Although, by not doing so, the Applicants do not accede that there is not further basis for establishing the nonobviousness of the dependent claims above and beyond what has already been presented. Therefore, the Applicants reserve the right to establish the nonobviousness of each and every dependent claim in future remarks or comments.

Pursuant to the above amendments and remarks, consideration and allowance of the pending application is believed warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

Credit Card Payment Form PTO-2038 authorizing payment in the amount of $1,112 ($920 for 3 months extension of time and $192 for additional claims) is enclosed. This amount

is believed to be correct; however, the Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No.14-0629.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Gwendolyn D. Spratt — Date: 6-26-02

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Marked-up Copy of Claims showing Changes Made

7. (Twice amended) A mosaic polypeptide comprising one or more antigenic epitopes of each of the hepatitis C virus (HCV) [HCV] core protein, nonstructural protein 3 (NS3 protein)[NS3 protein], and nonstructural protein 4 (NS4 protein), wherein at least two antigenic epitopes are from the same region of variants of the same protein [NS4 protein].

13. (Twice amended) The mosaic polypeptide of Claim 8, wherein the antigenic epitope of the NS5a protein comprises amino acid residues 2322-2423 of the HCV polyprotein. [comprises amino acid residues 1471-1573 of the HCV polyprotein.]